UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

HL

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/126,816	07/31/98	VON EICHEL-STREIBER	C	PM254992

HM22/0105

PILLSBURY MADISON & SUTRO
1100 NEW YORK AVENUE NW
NINTH FLOOR EAST TOWER
WASHINGTON DC 20005-3918

EXAMINER	
BURKE, J	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 01/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/126,816	Applicant(s) Von Eichel-Streiber et al
	Examiner Julie E. Burke, (Reeves), Ph.D.	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-11* is/are pending in the application.

Of the above, claim(s) *1-6 and 11* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *7-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-6 and 11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected Inventions. Election was made **without** traverse in Paper No. 8.

2. Claims 1-11 are pending. Claims 7-10 are elected and under examination.

Compliance with the Sequence Requirements

3. This application contains a sequence disclosure on page 20 of the specification that is encompassed by the definitions for nucleic acid and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, the specification fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide And/or Amino Acid Sequence Disclosures.

4. Applicant is given the time allotted in this Office Action within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821 (g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Drawings

5. The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(i), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Specification

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

8. The disclosure is objected to because of the following informalities:

a. the priority claimed for PCT/EP97/000426 is not recited in the first line of the specification.

b. The Brief Description of the Drawings, pages 13-14, is incomplete as it lacks a separate description for Figures 4, 6 and 7. The Brief Description of the Drawings needs to be amended so that Figures 4, 6 and 7 recite separate descriptions for each view (i.e, Fig. 4A, Fig. 4B, etc.) that match the labels for the Drawings. Accordingly the brief description of the drawings should reflect this change in the numbering scheme. Also any reference to the figures should reflect the new numbering scheme.

c. The terms "glycine" and "lysine" on page 1, second full paragraph, are apparently misspelled.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

9. Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 7-10 are indefinite for reciting "LT" . Full terminology should be in first instance of the claims with the additional use of the abbreviation in parentheses. Abbreviations may then be used in the dependent claims. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

b. Claim 7 is indefinite for reciting "characterized by activation of Ras proto-oncoproteins' because it is not clear whether the composition or the condition is characterized as such. Moreover, it is not clear to what extent the composition or condition are characterized as such. Claim 7 is indefinite for reciting "comprising a first part, a second part and a third part" because it is not clear whether the oncoproteins, the condition or the composition comprising the three parts. As written the claim does not have proper antecedent basis for the terms.

c. Claims 7-10 are indefinite for reciting "the first part including" because it is not clear what else is included in the first part, for example. Amending the claim to recite a "first part comprising", for example, would be sufficient to obviate this indefiniteness. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

d. Claim 7, part (i) is indefinite for reciting "the immunotoxin" and "said patient's cell" because proper antecedent basis is lacking for these terms.

e. Claim 7, part (ii) is indefinite for reciting "the cytoplasmic membrane of the cell" because proper antecedent basis is lacking for the terms "cell" and cytoplasmic membrane".

f. Claim 8, part (i) is indefinite for reciting "said patient's cell" because proper antecedent basis is lacking for this term.

g. Claim 9 is indefinite for reciting "characterized in that the target cell specific binding domain is an antibody" because it is not clear to what extent or how the immunotoxin is characterized.

h. Claim 9 is indefinite for reciting "an active fragment thereof" because it is not clear what sort of activity the fragment has-- antigen binding fragment, an effector function, metabolic activity, etc. Amending the claim to recite an antigen binding fragment thereof would be sufficient to obviate this rejection.

i. Claim 10 is indefinite for reciting "characterized by combining" because it is not clear to what extent or how the method is so characterized. Replacing the terms "characterized by" with "said method comprising" would be sufficient to obviate this rejection.

j. Claim 10 is indefinite for reciting "therapeutically useful amount" The phrase "effective amount" is indefinite when the claims fail to state the function which is to be achieved. See In re Frederiksen & Nielsen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). While the term "therapeutically" modifies "effective", it is not clear whether a preventive vaccine or a it is impossible to determine the endpoint (vaccination, inhibition, augmentation, pain reduction, etc) to be achieved.

10. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunotoxin fusion protein comprising an antibody or antigen binding fragment thereof, a translocation domain capable of translocating the LT catalytic domain across

the cytoplasmic membrane of a cell and the Clostridium sordellii Lethal toxin (LT) catalytic domain, composition comprising such a method of manufacturing compositions comprising the immunotoxin and a therapeutically acceptable adjuvant or carrier, does not reasonably provide enablement for compositions comprising any target cell specific binding domain, or any active fragment of an antibody, any polypeptide with the toxic activity of the catalytic domain of the toxin LT from Clostridium sordellii LT, manufacture of therapeutic agents and combining therapeutically useful amounts of an immunotoxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claim broadly recite any composition for treating any pathological condition characterized by activation of Ras onco-proteins, wherein the composition comprises any target cell specific binding domain, including an active fragment of an antibody, a translocation domain and a polypeptide with the toxic activity of the catalytic domain of toxin LT from Clostridium

sordellii LT. The claims also broadly recite a method of manufacturing a therapeutic agent by combining a therapeutically useful amount of an immunotoxin with a carrier or adjuvant.

c. The specification teaches that Clostridium sordellii produces two toxins, HL and LT (pages 2-3 bridging paragraph) and that LT has the ability to glucosylate Ras' threonine 35 (page 4, third full paragraph). The specification teaches that although toxins A and B of C. difficile, are, in regard to their sequence largely homologous to LT, inactivate only small G-proteins of only the Rho subfamily (page 4, first full paragraph). The claims broadly recite using any polypeptide with the toxic activity of the catalytic domain of toxin LT from Clostridium sordellii LT. The specification has not enabled any other molecules which have this activity besides the LT of Clostridium sordellii. It would require one skilled in the art undue experimentation to determine which polypeptides also have the exact same activity of the Clostridium sordellii LT. Amending the claims to recite wherein the third part comprises the LT toxin of Clostridium sordellii LT would be sufficient to obviate this portion of the rejection.

d. The claim recite any target cell specific binding domain, wherein it is characterized as an antibody or an active fragment of an antibody. The specification has only enabled using the heavy and light chain variable regions of an antibody as the target cell specific binding domain. Although the constant regions of an antibody are considered 'active fragments' in view of their ability to enhance effector functions, only the variable domains would specifically bind an antigen. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody,

each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986). The immunotoxin comprising only an active fragment would not be able to specifically bind antigen as required by the claims. Amending the claims to recite wherein the target cell specific binding domain is an antibody or antigen binding fragment thereof would be sufficient to obviate this portion of the rejection.

e. The claim 10 recites combining a therapeutically useful amount of an immunotoxin with a carrier or adjuvant. The claim is silent concerning what use the immunotoxin will have. While the term "therapeutically" modified "useful", the specification does not support the use of broadly claimed immunotoxins for the broad scope for all the possible therapies. See In re Frederiksen & Nielsen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). Amending the claim to delete the phrase "therapeutcially useful" would obviate this portion of the rejection.

Priority

11. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under domestic or foreign priority as follows: copies of the PCT and the EPO parent documents are not present in the file. Therefore, the Examiner is unable to determine whether the instant claims are to be granted priority back to the dates claimed.

Claim Rejections - 35 U.S.C. § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 7-8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by any of Popoff (Infection and Immunity Vol 55(1)35-43 1987) or Roberts et al (WO/9422476 published 13 Oct 1994) as evidenced by Chaves-Olarte et al (J Biol Chem Vol 274 No 16 11046-11052 4/99).

a. Claim 7-8 and 10 recite an immunotoxin comprising a targeting cell specific binding domain, a translocation domain and a polypeptide with the toxic activity of the catalytic domain of toxin LT from Clostridium sordellii LT; compositions comprising such and a method of manufacturing compositions comprising such. Applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02], therefore, the phrases "useful in treating a pathological conditions" "therapeutic agent" containing a "therapeutically useful amount of an immunotoxin" are not given patentable weight for this rejection. It is noted that the term "immunotoxin" in claims 7-8 and 10 is given no patentable weight because the claims do not recite which part of the composition has anything to with the immune system.

b. Popoff teach a homogenous LT preparation characterized as a single band on silver stained SDS polyacrylamide gels (page 42, col 1, fifth full paragraph). Popoff teach that the purified LT was lethal for mice (page 40, first full paragraph). Popoff teach a composition comprising the purified LT in the therapeutically acceptable carrier or adjuvant PBS (page 36, col 1, fifth full paragraph).

c. Roberts et al teach vaccines comprising toxoids derived from Clostridium sordellii and a saponin adjuvant (page 2, lines 28-33). Roberts et al's Clostridium sordellii composition would inherently comprise the LT toxin.

d. As evidenced by Chaves-Olarte et al, either of Roberts et al's or Popoff 's lethal toxins of Clostridium sordellii (LT or also known as TcsL, see page 11046, abbreviations and bridging paragraph cols 1-2) contain a catalytic domain (a polypeptide with the toxic activity of the catalytic domain of toxin LT from Clostridium sordellii LT), a hydrophobic domain (translocation domain) and a receptor binding domain (the target cell specific binding domain) as shown in the Schematic representation of TcsL-1552. Fig 1). Thus the limitations of the claims have been met.

14. Claims 7-8 and 10 are rejected under 35 U.S.C. 102(a or b) as being anticipated by any of Green et al (Gene 161:57-61 1995) or von Eichel-Streiber et al (Mol Microbiol Vol 17(2) 313-321 1995) as evidenced by Chaves-Olarte et al (J Biol Chem Vol 274 No 16 11046-11052 4/99).

a. The claims have been described above. The evidence provided by Chaves-Olarte et al has been described above.

b. In view of the fact that the priority documents are missing and in view of the fac the exact date of publication for the Green et al and von Eichel-Streiber references were not available at the time this Office Action was produced, the rejection is made under both 35 U.S.C.

102(a) and 35 U.S.C. 102(b). Once the priority date and reference publication dates are available, the rejection will be amended accordingly.

c. Green et al teach cloning and characterization of the cytotoxic L-encoding gene of Clostridium sordellii. The open reading frame shows a highly conserved hydrophobic domain (translocation domain) and a highly conserved carboxyl terminal.

d. Von Eichel-Streiber et al teach that the immunologically, ToxA and ToxB of C dificils are related to lethal toxin of Clostridium sordellii (page 313, col 2, second full paragraph). Von Eichel-Streiber et al teach that "morphological changes induced by the ToxB-1470 protein and LT of C. Sordellii were indistinguishable"(page 317, col 1, last paragraph; Fig 4) and that the cytopathic effects of ToxB-1470 are indistinguishable from those caused by the lethal toxin of Clostridium sordellii (see Abstract). Von Eichel-Streiber teaches that the toxins of C. Difficile contain a amino terminal toxic domain, an intermediary translocation domain and a final C terminal region contributing to cellular binding and that this organization resembles that of other bacterial toxins including all clostridium neurotoxins (page 319, final paragraph).

Claim Rejections - 35 U.S.C. § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Popoff (supra) or von Eichel-Streiber et al (supra) in combination with Blakey et al (Antibody Toxin Conjugates: A Perspective. Waldmann H. (ed): Monoclonal Antibody Therapy. Prog. Allergy. Basel, Karger, 1988 vol. 45 pp 50-90).

a. Claim 8 has been described above. Claim 9 recites an immunotoxin characterized in that the target cell specific binding domain is an antibody or an active fragment thereof.

b. Both of Popoff or von Eichel-Streiber et al have been discussed above, individually, with regards to the Clostridium sordellii LT toxin. However, none of Popoff (supra) or von Eichel-Streiber et al provide the methods to conjugate the toxin to an antibody to create the claimed immunotoxin.

c. Blakey et al describe the rationale and methods for coupling antibodies to toxins for pharmaceutical therapy. In particular, Blakey et al disclose conjugating bacterial toxins (see Figs 2 and 3) to antibodies specific for tumour associated antigens.

d. It would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to have chemically conjugated any of the prior art's Clostridium sordellii LT to antibodies or active fragments thereof directed against tumour associated antigens (TAA), as described by Blakey et al. Further, one skilled in the art would have been motivated to add a toxin to the anti-TAA antibody for the express purpose of creating a anti-TAA immunotoxin and, given the rationale provided by Blakey et al, one would have had a reasonable expectation of success in coupling a toxin to an antibody. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The chemical linkages produced by Blakey et al's methods would comprise covalent bonds as required by the claims. Therefore the invention, as a whole, was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

19. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al in combination with either of Vitetta et al (Science Vol 238:1038 11/87) or Sandhu (Critical reviews in Biotechnology Vol 12(5/6) 437-462 1992)

a. Claims 8-9 have been described above.

b. Green et al has been discussed above with regards to the Clostridium sordellii LT toxin and the C. Dificille cytotoxin B. Green et al fails to provide the methods to make a fusion protein comprising the LT or ToxB toxin and an antibody to cell specific binding domain to create the claimed immunotoxin. However this deficiency is made up for by the teachings of either of Vitetta et al or Sandhu et al.

c. Vitetta et al teach that the development of third generation IT [immunotoxins] as produced by recombinant DNA technology would be advantageous to prepare homogenous IT's (page 1103, cols 1-2, bridging paragraph). Vitetta et al teach in general that the DNA encoding the toxin region could be fused to DNA encoding the antigen combining region of an antibody. Vitetta et al teach that antibodies may be directed against determinants on neoplastic cells (pages 1098-9 bridging paragraph). Vitetta et al teach that by cloning genes for relevant toxins and antibodies and manipulating these genes, nature's molecules can be redesigned in a more rational manner. 9B

d. Sandu teach that bacterial toxins have been used in developing targeting toxins for the treatment of c- .r (page 455, first full paragraph). Sandhu teach using recombinant DNA technology to synthesize antibody/toxin fusion proteins in E. coli. Sandhu teach that these 9B 8 of Dec 99

fusion proteins selectively kill cells bearing the appropriate antigens and provide motivation for making immunotoxins for the treatment of cancer (page 455, col 2 second full paragraph).

e. It would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to have used recombinant DNA technology to ligate DNA encoding any of the Green et al's Clostridium sordellii LT to DNA encoding antibodies or active fragments thereof directed against tumour associated antigens (TAA), as described by either of Vitetta et al or Sandhu. Further, one skilled in the art would have been motivated to add a toxin to the anti-TAA antibody for the express purpose of creating a anti-TAA immunotoxin and, given the rationale provided by either of Vitetta et al or Sandhu, one would have had a reasonable expectation of success in using recombinant DNA technology to couple a toxin to an antibody. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The peptide linkages produced by either of either of Vitetta et al or Sandhu's methods would comprise covalent bonds as required by the claims. Therefore the invention, as a whole, was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Burke, née Reeves, Ph.D, whose telephone number is (703) 308-

7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie E. Burke, née Reeves, Ph.D.

Primary Patent Examiner

(703) 308-7553

JULIE BURKE
PRIMARY EXAMINER